REMARKS

Reconsideration of the above-identified application in view of the present amendment is respectfully requested.

1. Claim Objections

Claim 4 was objected to because of the phrase "the transduced human progenitor cells" is dependent on claim 5 which recites "transformed human hematopoietic progenitor cells". Claim 4 has been amended to recite "transformed human progenitor cells" and is now consistent with Claim 5.

2. 35 U.S.C. §102(b) rejection of claims 3-5.

Claims 3-5 were rejected under 35 U.S.C. §102(b) as being anticipated by Reese et al. (Proc. Natl. Acad. Sci. 93:14088-14093, 1996) as evidenced by Prockop, D.J. (Science 276:71-74, 1997). The Office Action argues that Reese et al. teaches the transduction of mutant methylguanine DNA methyltransferase gene into human CD34 cells co-cultured on a human bone marrow stroma. The Office Action further argues that it is apparent to one skilled in the relevant art that the bone marrow human stroma contains passaged, irradiated and adhered bone marrow mononuclear cells, and that this cell population encompasses isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop. The Office Action also argues that since Prockop teaches cells isolated by their adherence to plastic in the absence of non-adherent cells and used as feeder layers for hematopoietic stem have many of the characteristics of MSCs, that they are equivalent to homogenous populations of isolated mesenchymal stem cells of the present application.

The Examiner also argues in response to Applicant's previous argument put forth that neither Reese et al. nor Nolta et al. disclose the co-culturing of human hematopoietic stem cells with exogenous genetic material in the presence of the isolated human mesenchymal stem cells. The Examiner argues that the passaged, irradiated human bone marrow stromal cell population used in Reese et al., Nolta et al., and Wells et al., are isolated mesenchymal stem cells which are equivalent to the isolated mesenchymal stem cells of the present invention as evidenced by the teachings of Prockop.

Claim 5 has been amended to recite "…co-culturing human hematopoietic progenitor cells with human mesenchymal stem cells isolated from human mesoderm tissue…" Support for this limitation can be found on page 5, first paragraph, of the Application.

Claim 5, as amended, is not anticipated by Reese et al. because Reese et al. do not teach the co-culturing of human hematopoietic progenitor cells with human mesenchymal stem cells isolated from human mesoderm tissue. Reese et al. teach the culture of retroviral infected hematopoietic cells on human bone marrow stroma, a human mesoderm tissue. Although bone marrow human stroma may include some mesenchymal stem cells, bone marrow human stroma is not equivalent to mesenchymal stem cells which have been isolated from human mesoderm tissue. Additionally, the Examiner has provided no evidence to support the assertion that bone marrow human stromal is equivalent to mesenchymal stem cells isolated from human mesoderm tissue. Isolated mesenchymal stem cells are distinguished from marrow stroma given that MSCs are distinct in morphology and lack surface markers

for T and B lymphocytes, macrophages and endothelial cells (see Application pg. 5, lines 14-17). Reese et al., at best teach the culture of hematopoietic cells on a heterogeneous mesodermic tissue. Reese et al. do not teach MSCs isolated from such a mesodermic tissue.

Accordingly, Applicants respectfully request that the 35 U.S.C. §102(b) rejection of claim 5 be withdrawn because Reese et al. as evidenced by Prockop do not teach all the limitations of claim 5. Claims 3 and 4 depend either directly or indirectly from claim 5, and therefore should be allowed because of the aforementioned deficiencies in the rejection with respect to claim 5 and because of the specific limitation recited in claims 3 and 4.

Claims 3-5 were also rejected under 35 U.S.C. §102(b) as being anticipated by Nolta et al. (Blood 86:101-110, 1995) as evidenced by Prockop, D.J. (1997)

The office action argues that Nolta et al. discloses a transduction method for human CD34 cells in the presence of a stroma generated by human allogeneic bone marrow stromal cells. The Office Action further states that the bone marrow stromal cell population contains isolated mesenchymal stem cells as evidenced by the teachings of Prockop as described above.

As discussed above, Claim 5 has been amended to recite "…co-culturing human hematopoietic progenitor cells with human mesenchymal stem cells <u>isolated from human mesoderm tissue</u>…"

Nolta et al. teach the transduction of CD34 cells with retroviral vectors in the presence of a stroma generated by human allogeneic bone marrow stromal cells, a human mesoderm tissue. Although bone marrow derived human stroma may

include some mesenchymal stem cells, bone marrow human stroma is not equivalent to mesenchymal stem cells which have been isolated from human mesoderm tissue. Isolated mesenchymal stem cells are distinguished from marrow stroma given that MSCs are distinct in morphology and lack surface markers for T and B lymphocytes, macrophages and endothelial cells (see Application pg. 5, lines 14-17). Nolta et al., at best teach the culturing of CD34 cells in the presence of a mesodermic tissue. Nolta et al., like Reese et al. do not teach MSCs isolated from such a mesodermic tissue.

Accordingly, Applicants respectfully request that the 35 U.S.C. §102(b) rejection of claim 5 be withdrawn because Nolta et al. as evidenced by Prockop do not teach all the limitations of claim 5. Claims 3 and 4 depend either directly or indirectly from claim 5, and therefore should be allowed because of the aforementioned deficiencies in the rejection with respect to claim 5 and because of the specific limitation recited in claims 3 and 4.

Claims 2 and 4-5 were also rejected under 35 U.S.C. 102(b) as being anticipated by Wells et al., (Gene Therapy 2:512-520, 1995) as evidenced by Prockop. The office action argues that Wells et al. discloses a transduction method for human bone marrow CD34 progenitor cells in the presence of an autologous bone marrow stromal support containing isolated mesenchymal stem cells as evidenced by the teachings of Prockop as described above.

Amended Claim 5 of the present invention is not anticipated by Wells et al. because like Nolta et al. and Reese et al., Wells et al. does not teach the co-culturing human hematopoietic progenitor cells with human mesenchymal stem cells isolated

from human mesoderm tissue…". At best Wells et al. teach the culturing of CD34 cells in the presence of a mesodermic tissue.

Accordingly, Applicants respectfully request that the 35 U.S.C. §102(b) rejection of claim 5 be withdrawn because Wells et al. as evidenced by Prockop do not teach all the limitations of claim 5. Claims 2 and 4 depend either directly from claim 5, and therefore should be allowed because of the aforementioned deficiencies in the rejection with respect to claim 5 and because of the specific limitation recited in claims 2 and 4.

Claim 5 is also allowable because the Examiner's response to Applicant's previous arguments fails to show that claim 5 is anticipated by Reese et al. or Nolta et al. The bone marrow stromal cell population co-cultured in the presence of human hematopoietic stem cells in Reese et al., Nolta et al., and Wells et al. as evidenced by Prockop, are not equivalent to the isolated mesenchymal stem cells in claim 5 of the present invention.

Prockop states that adherent marrow stromal cells have many of the characteristics of mesenchymal stem cells. However, the populations of cells isolated by adherence to plastic are described as initially heterogeneous and difficult to clone (pg. 72, col 2). The fraction of hematopoietic cells in the cell population isolated by their adherence to plastic is described as relatively high in initial cultures of mouse marrow and less than 30% with human marrow (pg. 72, col. 3).

Prockop also states that a more homogeneous population of isolated cells holds advantages over those isolated by adherence to plastic. For instance, Prockop states that when more homogenous populations of cells are either clonal or

near clonal, they express small amounts of bone cell markers and can be induced in culture to express large amounts of the same markers (pg. 72, col. 2). Additionally, Prockop states that several groups of investigators have attempted to prepare more homogenous populations of mesenchymal stem cells instead of what is described by Prockop as the "crude procedure" (pg. 72, col. 1) of isolating mesenchymal stem cells by adherence to plastic.

Furthermore, the Prockop reference states that although the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of mesenchymal stem cells, which are isolated by their adherence to plastic in the absence of non-adherent cells, it is not clear if the adherent cells contain true mesenchymal stem cells. Prockop states that it is uncertain that the adherent feeder cells retain the potential to differentiate into bone, cartilage, and other mesenchymal cells. Prockop even suggests that the adherent cells may have differentiated into another and discrete phenotype because of their continuing interaction with hematopoietic cells (pg. 72, col. 3).

As discussed above, the present application the mesenchymal stem cells represent a well characterized isolated cell population which can be prepared in a reproducible manner compared to heterogeneous stromal cell cultures. As discussed in Prockop, these heterogeneous stromal cell cultures contain T and B lymphocytes, macrophages, dendritic cells and endothelial cells. The mesenchymal stem cells of the present Application can be distinguished from the more complex cellular environment present in adherent cells of long-term bone marrow stromal cultures.

The isolated mesenchymal stem cells for use in present invention are described as isolated and prepared using procedures described in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584 (see Application, pg. 5, lines 2-5). This morphologically distinct homogenous isolated mesenchymal stem cell population is not isolated and prepared using the crude plastic adherence methods described in Prockop. For example the human mesenchymal stem cells for use in the present invention may be isolated using a density gradient fractionation or selective antibody purification.

The Office Action fails to show that the heterogeneous adherent bone marrow stromal cells used as feeder layers for hematopoietic stem cells of Prockop are equivalent to the isolated mesenchymal stem cells of the present application. Therefore, the Office Action has failed to teach the use of mesenchymal stem cells isolated from human mesoderm tissue co-cultured with human hematopoietic progenitor cells.

Accordingly, Applicants respectfully request that the 35 U.S.C. §102(b) rejection of claim 5 be withdrawn because Reese et al., Nolta et al., and Wells et al., as evidenced by Prockop do not teach all the limitations of claim 5.

In view of the forgoing, it is respectfully submitted that the above-identified application is in condition for allowance, and allowance of the above identified application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this amendment to our Deposit Account No. 20-0090.

Respectfully submitted,

/Richard A. Sutkus/
Richard A. Sutkus
Reg. No. 43,941

TAROLLI, SUNDHEIM, COVELL,
& TUMMINO L.L.P.
1300 East Ninth Street, Suite 1700
Cleveland, Ohio 44114
Phone:(216) 621-2234
Fax: (216) 621-4072
Customer No.: 68,705